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Egg consumption and risk of incident type 2 diabetes: a dose–response meta-analysis of prospective cohort studies

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Abstract

Experimental data suggest that egg intake could have a beneficial impact on several risk factors for type 2 diabetes. In contrast, some recent epidemiological studies have concluded that egg consumption may increase diabetes risk. We performed a dose–response meta-analysis of prospective cohorts on the relation of egg consumption with incident type 2 diabetes. We searched for cohort studies that assessed egg consumption and diabetes risk up to June 2015. We identified 416 articles and extracted data independently and in duplicate from ten eligible studies. We used random-effects generalised least squares models for pooled dose–response estimation based on thirteen estimates. Our study included 251 213 individuals and 12 156 incident type 2 diabetes cases. Egg intake was associated with incident type 2 diabetes (risk ratio (RR)/egg per d 1·13; 95 % CI 1·04, 1·22). We identified study location as a major source of heterogeneity. For studies conducted in the USA, we observed a stronger association (RR 1·47; 95 % CI 1·32, 1·64), whereas results were null for studies conducted elsewhere. Studies considered to be of high quality yielded null findings (RR 0·94; 95 % CI 0·74, 1·19). The association of egg intake with increased risk of incident type 2 diabetes may be restricted to US cohort studies. There are limited data to support a biological mechanism that could underlie this association; thus, the possibility that these results may be due to residual confounding by dietary behaviours restricted to certain populations cannot be excluded.

Key words: **Diets: Nutrition: Diabetes mellitus: Cohorts**

In observational studies, cholesterol intake has been associated with impaired glucose metabolism[1] and type 2 diabetes risk[2,3]. Preliminary results from small randomised-controlled trials have shown that adding eggs, an important source of dietary cholesterol, to the diet improved insulin sensitivity[4] and atherogenic lipoprotein profile[4,5] and decreased inflammatory markers[6,7]. Furthermore, observational data support the role of circulating small and dense LDL and HDL particles[8] and inflammation[9] on diabetes risk. However, other nutrients found in eggs (e.g. choline) could also play a role in diabetes risk[10–12]. In contrast, a previous meta-analysis of epidemiological studies concluded that egg consumption may increase diabetes risk[13]. Owing to the absence of randomised trials directly assessing the effect of egg consumption on type 2 diabetes, we conducted a dose–response meta-analysis of prospective cohort studies to quantify the association between habitual egg intake and risk of type 2 diabetes.

Methods

Search strategy

We followed standard criteria for conducting and reporting meta-analyses of observational studies[14]. We searched for all prospective cohort studies that evaluated egg consumption and risk of diabetes mellitus in adults from the earliest available online indexing through June 2015. We conducted our study search without language restrictions on MEDLINE (egg[tw] or eggs[tiab] or 'animal food'[tiab]) and ('diabetes mellitus'[mesh] or diabetes[tiab]), EMBASE and EBSCOhost; we reviewed related articles, hand searched reference lists and directly contacted the authors. The search key words were 'eggs', 'animal food' and 'diabetes mellitus'. One investigator (M. T.) screened titles and abstracts, and two investigators (M. T., M. L.) independently and in duplicate reviewed full texts of potentially relevant articles and assessed study eligibility. We included

Abbreviation: RR, risk ratio.

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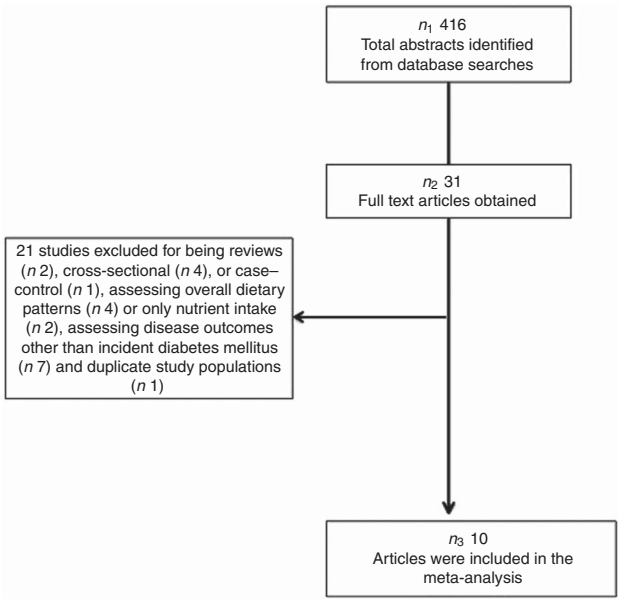

Fig. 1. Flow diagram of the study selection process.

studies that provided multivariable-adjusted risk estimates. We resolved differences by consensus. *A priori* we excluded ecological and cross-sectional analyses, case–control studies, commentaries, general reviews and case reports (Fig. 1). When duplicate studies were present, we chose the most recent publication. We also excluded studies reporting only crude risk estimates. After screening titles and abstracts of 416 articles and reviewing thirty-one full-texts, we extracted study characteristics and data in duplicate from ten eligible studies[15–24] (Fig. 1) with a total of thirteen estimates. Thus, twenty-one studies were excluded because they were reviews (n 2)[25,26], cross-sectional (n 4)[27–30] or case–control (n 1)[31]studies; assessed overall dietary patterns (n 4)[32–35] or nutrient intakes (n 2)[36,37]; included participants with prevalent disease (n 4)[38–41] or gestational diabetes (n 1)[42] or other outcome different from diabetes (n 2)[43,44]; or because of duplicate study population (n 1)[45].

Data extraction

We extracted data using a standard electronic form independently and in duplicate by two investigators (M. T., M. L.). Information included the first author's name, contact information, year of publication, number of years the study was performed, study name, study location, population (age, sex, race, exclusion criteria and sample size), mean age and standard deviation at baseline, duration of follow-up, exposure assessment, egg consumption categories, outcome definition, outcome ascertainment, covariates adjusted for, number of participants, person-years, number of events and adjusted risk estimates and 95 % CI. When the mean age of the total study population was unavailable, we calculated the weighted mean age and weighted standard deviation based on exposure categories' specific information. We assumed one serving of egg to be equivalent to 50 g. We gave preference to multivariable estimates from models with the greatest control for potential confounders. Hazard ratios and OR were assumed to approximate risk ratios (RR). We assigned studies a degree of covariate adjustment: minimal (socio-demographic covariates), adequate (socio-demographic plus either other risk factors or dietary variables) and optimal (socio-demographic plus risk factors and dietary variables). Issues regarding missing data or definitions were resolved by direct contact with authors.

We assessed study quality based on the degree of covariate adjustment and the Newcastle–Ottawa quality assessment scale for observational studies in meta-analyses[46]. This scale for observational studies in meta-analyses grants a maximum of 9 points to each study: a maximum of 1 point for each item within the selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study) and outcome categories (assessment of outcome, length of follow-up, adequacy of follow-up) and a maximum of 2 points for the comparability category based on the design or analysis. We assigned scores of 0–6 for low-quality and 7–9 for high-quality studies based on the distribution of scores among studies. Differences in quality assessment scores between investigators were unusual and were resolved by consensus.

Statistical analyses

We conducted random-effects, dose–response regressions by using generalised least squares for trend estimation (one-stage estimation)[47]. We assumed hazard ratios and OR-approximated RR. Covariance was fit with the use of total numbers of cases plus non-cases for studies that reported OR or person-years for studies that reported RR or hazard ratios, at each level of exposure. For completeness, we also performed two-stage estimation: separate generalised least squares models for trend were evaluated for each study to derive study-specific, log-linear dose–responses (log RR), and then each study-specific log RR was pooled in a second generalised least squares model for trend. We pre-specified one-stage estimation as our primary outcome because it uses all available estimates in each study yielding a better estimate of the variance–covariance matrix relative to the two-stage estimation. We tested the between-study heterogeneity with goodness of fit (χ^2). When exploring dietary factors in relation to diabetes, BMI is commonly included in models to adjust for confounders. However, this variable could also be considered an intermediate in the causal pathway. Therefore, we conducted sensitivity analyses including (when available) estimates from models that were not adjusted for BMI. We explored *a priori* potential sources of heterogeneity by using meta-regression (sex, study location (USA *v.* Europe/Asia), study quality (Newcastle–Ottawa score <7 or ≥7), years of follow-up (<15, ≥15), mean age (<50, ≥50 years) and method for assessing dietary intakes (FFQ *v.* other methods)). We constructed funnel plots for visual inspection of publication bias and evaluated statistically the bias using Begg's test[48]. Finally, we stratified the data by sex, study location and quality score. Analyses were performed using Stata 11.2 for Mac (StataCorp LP), with two-tailed $\alpha < 0{\cdot}05$. Analytical code used is provided in the online

Supplementary Material, and databases and documentation are available as supplemental digital content.

Results

We identified ten studies with thirteen different estimates that included 251 213 individuals (173 463 women and 77 750 men) and 12 156 incident cases of type 2 diabetes. The studies were conducted in the USA (*n* 4), Asia (*n* 1) and Europe (*n* 5). Age ranged from 38 to 95 years, and the median daily egg consumption ranged from 0 to 1·1 eggs across studies (Table 1). Nearly all studies adequately adjusted for important diabetes risk factors including age, sex, BMI, smoking status, alcohol use, physical activity and dietary factors.

Each egg per day was associated with a 13 % higher risk of incident type 2 diabetes (one-stage estimation RR 1·13; 95 % CI 1·04, 1·22; $P_{\text{heterogeneity}} < 0{\cdot}001$) (Fig. 2). In contrast, secondary results from the two-stage estimation (which does not use all available information) were null (RR 1·07; 95 % CI 0·93, 1·24). The results from a sensitivity analysis that used estimates that did not include BMI, a potential intermediate, were qualitatively the same (online Supplementary Fig. S1). Using meta-regression, we explored sources of heterogeneity: sex ($P = 0{\cdot}84$), mean age ($P = 0{\cdot}15$), study location ($P = 0{\cdot}03$), study quality ($P = 0{\cdot}18$), years of follow-up ($P = 0{\cdot}46$) and method for assessing dietary intakes ($P = 0{\cdot}20$). When we stratified the analyses by study location, we observed that in the studies conducted in the USA an egg per day was associated with a 47 % higher risk of type 2 diabetes (RR 1·47; 95 % CI 1·32, 1·64), whereas the association for studies conducted elsewhere was null (Table 2). Moreover, the association for high-quality studies was null (RR 0·94; 95 % CI 0·74, 1·19). We found no evidence of publication bias on the funnel plot or Begg's test ($P = 0{\cdot}46$) (Fig. 3).

Discussion

In a dose–response meta-analysis of ten publications of prospective studies using thirteen estimates, we observed a direct association between egg consumption and type 2 diabetes. We found evidence that results may be driven in part by studies conducted in the USA and by studies of a lower quality.

In animal studies, cholesterol intake has been associated with impaired glucose metabolism[49] and inflammation[50]. However, these studies generally use a very high dose of cholesterol, thus potentially limiting the applicability of results to humans. Eggs are important contributors of dietary cholesterol, raising concerns that egg consumption may affect cardiovascular health and diabetes risk. However, there is no clear relationship between dietary cholesterol consumption and serum cholesterol[39], although there seems to be significant heterogeneity in the response to cholesterol intake. In addition to genetic factors[51], for example, obesity and insulin resistance appear to affect cholesterol absorption[52,53]. In addition, experimental studies in humans have shown that increased egg intake has rather had a beneficial impact on several risk factors for type 2 diabetes, such as insulin resistance[4], inflammation[6,7,54] and lipid particle size[4,5]. However, a previous meta-analysis of prospective cohorts concluded that individuals who ate an egg or more per day had a 42 % higher risk of diabetes compared with individuals who never consumed eggs[13]. This meta-analysis was based on five cohorts, included US studies only and dose–response was not assessed[16–18].

Contrasting results from intervention studies and observational studies should take into account design limitations. Conducting randomised trials to evaluate the effects of foods can be challenging because of costs, difficulties in blinding individuals and non-compliance because of the length of time that is necessary to observe incidence of outcomes. For example, only short-term intervention studies on egg consumption using intermediate risk markers are feasible but do not necessarily reflect diabetes risk. Thus, in the absence of trials that use diabetes as the outcome, one strategy is to infer these effects from long-term prospective cohort studies. Besides the fact that these studies may not adequately reflect the question of the potential effect of altering food consumption, two key limitations are the potential for residual confounding and for misclassification of the exposure. Our results are based on individual studies where the potential for these two major limitations is always present, and therefore the results should be interpreted with caution.

The observation that the association could be driven by studies conducted in the USA may reflect the possibility that egg consumption may be confounded by behaviours or dietary habits associated with diabetes risk that are common in this population. For example, in the US studies, egg intake is often associated with smoking[17,18,21] or lower physical activity[17] or higher intake of red meat[17,18,21], whereas this is generally not observed in studies outside the USA[19,24]. However, although one study in France did find such associations with egg intake, it still reported null findings for the relation of egg intake and type 2 diabetes[23]. Food preparation methods (e.g. boiled or fried eggs, whole eggs or only egg whites) or concurrent consumption of other foods that may increase diabetes risk (e.g. home fries, bacon) may also account for a part of the differences, but such information is not available in these studies. Our results are consistent with a recently published meta-analysis[55], and the conclusion that the association was not present in non-US populations is strengthened by the inclusion in the current meta-analysis of an additional study from Finland. The importance of adequate designs, robust ascertainment of exposure and outcome and collection of information on potential confounding factors with as much detail as possible is further underscored by the observation that better quality studies were less likely to find an association between egg consumption and diabetes risk. We classified four studies as low quality mainly because diabetes was self-reported and the follow-up rate was inadequate or not described[16,17,20]. It is difficult to interpret why results of these studies differ from high-quality studies. However, three of these studies were conducted in the USA.

The possibility that the observed differences across populations are the result of underlying biological mechanisms is still present. Intestinal microbiota may vary across populations and there is evidence that intestinal flora affects the production of trimethylamine-N-oxide from dietary phosphatidylcholine

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Table 1. Characteristics of participants in included studies of egg consumption and type 2 diabetes risk

First author (year)	Country	Study name	Population	Consumption in the lowest category (median, eggs/week)	Consumption in the highest category (median, eggs/week)	Exposure assessment
Montonen (2005)[15]	Finland	FMCHES	Men and women living in Finland	1·6	5·7	At baseline using a dietary history interview
Vang (2008)[16]	USA	AMS and AHS	California Seventh-day Adventist adults	0·0	1·5	FFQ
Djoussé (2009)[17]	USA	PHS	US male physicians	0·0	7·5	At baseline and at 24, 48, 72, 96 and 120 months after randomisation using a simple abbreviated FFQ
		WHS	US female health professionals	0·0	7·5	At baseline using a 131-item validated FFQ
Djoussé (2010)[18]	USA	CHS	Men insured by Medicare in 4 US communities (Forsyth County, NC; Sacramento County, CA; Washington County, MD; Pittsburgh, PA)	0·0	7·0	At baseline using a 99-item picture-sort version of the National Cancer Institute FFQ, and updated during the sixth annual visit by using a FFQ
			Women insured by Medicare in 4 US communities (Forsyth County, NC; Sacramento County, CA; Washington County, MD; Pittsburgh, PA)	0·0	7·0	
Zazpe (2013)[19]	Spain	SUN Project	Spanish university alumni	0·5	4·5	At baseline using a 136-item semi-quantitative FFQ
Kurotani (2014)[20]	Japan	JPHC	Men from 6 public health centre areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa and Osaka) in Japan	1·1	7·7	Self-administered 147-item FFQ at baseline and every 5 years × 2
			Women from 6 public health centre areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa and Osaka) in Japan	1·0	7·0	
Djoussé (2015)[21]	USA	JHS	African-American adults residing in Jackson, MS	0·1	5·5	At baseline using a 158-item FFQ
Ericson (2015)[22]	Sweden	MDC	Women and men living in Malmö, Sweden	0·6	6·3	At baseline using an interview-based modified diet-history method
Lajous (2015)[23]	France	E3N	Women affiliated to a health insurance plan for teachers and their spouses in France	0·0	6·9	At baseline using a validated 208-item self-administered diet history questionnaire
Virtanen (2015)[24]	Finland	KIHD	Men from eastern Finland	1·9	6·4	Food record of 4 consecutive days

Disease ascertainment	Age (years)	Sample size	% women	Follow-up (years)	Number of events	Person-years	Pre-specified analysis	Adjustment	Quality score	Additional information
Social Insurance Institution's nationwide register	40–69	4304	47	23	383	84 328	Secondary	+++	8	Yes
Self-report	>30	8401	39	17	535	–	Secondary	+	4	Yes
Self-report on annual follow-up questionnaires	≥40	20 703	0	20	1921	414 389	Primary	+++	5	Yes
Self-report on annual follow-up questionnaires and telephone interviews, supplemental questionnaires or review of medical records from treating physicians	≥45	36 295	100	11·7	2122	423 474	Primary	+++	6	
Medication use was assessed at baseline and annually by medication inventory, and fasting glucose was measured during clinical examinations	65–95	1669	0	11·3	142	17 213	Primary	+++	8	Yes
		2229	100		171	26 856				
Supplementary questionnaire, and blinded review of medical records	20–90	15 956	58	6·6	91	–	Primary	+++	7	Yes
Medical records	40–69	27 248	0	5	672	–	Primary	+++	6	Yes
		36 218	100		493	–				
Blood, plasma measurements	21–95	3564	64	7·3	531	–	Primary	+++	7	Yes
7 national registries: regional Diabetes 2000 registry of Scania, Swedish National Diabetes Registry, Swedish National Inpatient Registry, the Swedish hospital-based outpatient care, the Cause-of-Death Registry and the Swedish Prescribed Drug Registry	45–74	26 930	61	14	2860	377 642	Secondary	+++	8	No
Supplementary questionnaire, and drug reimbursement database	40–65	65 364	100	13·8	1803	879 133	Primary	+++	7	No
Self-reported physician-set diagnosis of type 2 diabetes and/or fasting plasma glucose ≥7·0 mmol/l or 2-h oral glucose tolerance test plasma glucose ≥11·1 mmol/l at re-examination on 3 occasions and by record linkage to the national hospital discharge registry and to the Social Insurance Institution of Finland	60–81	2332	0	19·3	432	45 008	Primary	+++	9	Yes

FMCHES, Finnish Mobile Clinic Health Examination Survey; AMS, Adventist Mortality Study; AHS, Adventist Health Study; PHS, Physicians' Health Study; WHS, Women's Health Study; CHS, Cardiovascular Health Study; SUN, Seguimiento Universidad de Navarra; JPHC, Japan Public Health Center-based Prospective; JHS, Jackson Heart Study; MDC, Malmö Diet and Cancer Cohort; E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study.

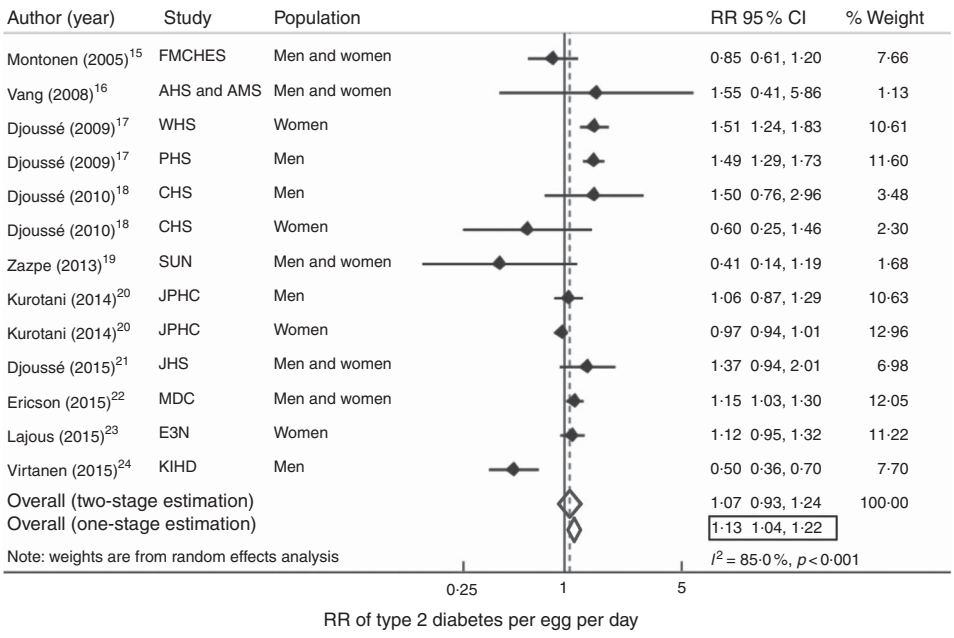

Fig. 2. Risk ratios (RR) of incident type 2 diabetes per egg per day. One-stage overall pooled dose–response estimate and 95 % CI are boxed. ◆ and —— Study-specific dose–response and 95 % CI; - - - - -, pooled dose–response; ◇, 95 % CI combining each study specific dose–response (two-stage); FMCHES, Finnish Mobile Clinic Health Examination Survey; AHS, Adventist Health Study; AMS, Adventist Mortality Study; WHS, Women's Health Study; PHS, Physicians' Health Study; CHS, Cardiovascular Health Study; SUN, Seguimiento Universidad de Navarra; JPHC, Japan Public Health Center-based Prospective; JHS, Jackson Heart Study; MDC, Malmö Diet and Cancer Cohort; E3N, Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; KIHD, Kuopio Ischemic Heart Disease Risk Factor Study.

Table 2. Consumption and risk of type 2 diabetes stratified by sex, study location and study quality (Risk ratios (RR) and 95 % confidence intervals)

Subgroup analyses	Number of estimates	RR	95 % CI	$P_{heterogeneity}$	I^2 (%)
Sex					
Men	4	1·03	0·66, 1·61	P < 0·001	91·7
Women	4	1·12	0·88, 1·41	P < 0·001	86·3
Men and women	5	1·07	0·84, 1·36	P = 0·12	45·6
Study location					
USA	6	1·47	1·32, 1·64	P = 0·53	0
Asia/Europe	7	0·95	0·83, 1·10	P < 0·001	79·1
Study quality score					
Low (0–6)	5	1·24	0·96, 1·59	P < 0·001	91·8
High (7–9)	8	0·94	0·74, 1·19	P < 0·001	76·7

(egg yolks are important contributors)[10]. In animal studies, this metabolite appears to play a role in glucose metabolism[12]. Thus, there is a need to further study this association between egg consumption and glucose metabolism across populations.

Our meta-analysis has several strengths. We systematically reviewed multiple databases for all prospective studies on egg consumption and diabetes risk. We contacted authors directly when clarifications of findings or additional data were necessary, thus minimising potential misclassification and publication bias. We performed study inclusion/exclusion and data extraction in duplicate and independently. We explicitly assessed dose–response rather than carrying out simple categorical comparisons using generalised least squares models for trend estimation.

Our results suggest that the association of habitual consumption of eggs and incidence of type 2 diabetes observed in

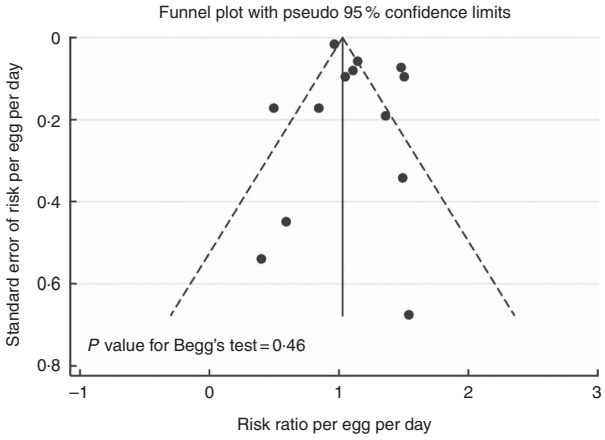

Fig. 3. Funnel plot for graphical assessment of potential publication bias.

prospective studies may be restricted to studies conducted in the USA. In the absence of a clear biological mechanism, the possibility that the observed relation may be due to residual confounding by dietary behaviours or food preparation methods restricted to this population is always present.

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M. L. and J. K. V. conceived the study. M. L. and M. T. extracted data and contacted authors. M. T. conducted the analysis. M. L., M. T. and J. K. V. wrote and revised the manuscript.

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Supplementary material

For supplementary material/s referred to in this article, please visit http://dx.doi.org/doi:10.1017/S000711451600146X

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